1.5.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished pharmaceutical product

INN Name: Temozolomide Capsules 20 mg

Trade Name: TEMOTERO 20

Strength: 20 mg

Pharmaceutical form: capsules

2. Qualitative and quantitative composition

Each capsule contains 100 mg of Temozolomide

For Excipients kindly refer to 6.1 list of excipients

3. Pharmaceutical form

Dosage form: Capsules

Description: Opaque, yellow cap & white body, size '4' hard gelatin capsules imprinted with '14' on cap and 'H' on body, filled with off white to pale pink granular powder

4. Clinical particulars

4.1 Therapeutic indications

Temozolomide is indicated for the treatment of:

- Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.

- Children from the age of three years, adolescents and adult patients with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy

4.2 Posology and method of administration

Temozolomide should only be prescribed by physicians experienced in the oncological treatment of brain tumours.

Anti-emetic therapy may be administered.

Posology

Adult patients with newly-diagnosed glioblastoma multiforme

Temozolomide is administered in combination with focal radiotherapy (concomitant phase)

followed by up to 6 cycles of Temozolomide monotherapy (monotherapy phase).

Concomitant phase

Temozolomide is administered orally at a dose of 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions). No dose reductions are recommended, but delay or discontinuation of Temozolomide administration should be decided weekly according to haematological and non-haematological toxicity criteria. Temozolomide administration can be continued throughout the 42 day concomitant period (up to 49 days) if all of the following conditions are met:

- absolute neutrophil count (ANC) ≥ 1.5 x 10^9/l
- thrombocyte count ≥ 100 x 10^9/l
- common toxicity criteria (CTC) non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea and vomiting).

During treatment a complete blood count should be obtained weekly. TEMOZOLOMIDE administration should be temporarily interrupted or permanently discontinued during the concomitant phase according to the haematological and non-haematological toxicity criteria as noted in Table 1.

Table 1. Temozolomide dosing interruption or discontinuation during concomitant radiotherapy and Temozolomide

Toxicity	Temozolomide interruption[a]	Temozolomide discontinuation
Absolute neutrophil count	≥ 0.5 and < 1.5 x 10^9/l	< 0.5 x 10^9/l
Thrombocyte count	≥ 10 and < 100 x 10^9/l	< 10 x 10^9/l
CTC non-haematological toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

a: Treatment with concomitant Temozolomide can be continued when all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9/l; thrombocyte count ≥ 100 x 10^9/l; CTC non-haematological toxicity ≤ Grade 1 (except for alopecia, nausea, vomiting).

Monotherapy phase

Four weeks after completing the Temozolomide + RT concomitant phase, Temozolomide is administered for up to 6 cycles of monotherapy treatment. Dose in Cycle 1 (monotherapy) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 if the CTC non-haematological toxicity for Cycle 1 is Grade ≤ 2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/l, and the thrombocyte count is ≥ 100 x 10^9/l. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. Once escalated, the dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. Dose reductions and discontinuations during the monotherapy phase should be applied according to Tables 2 and 3.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose of Temozolomide). The dose should be reduced or administration discontinued according to Table 3.

Table 2. Temozolomide dose levels for monotherapy treatment

Dose level	Temozolomide dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 3. Temozolomide dose reduction or discontinuation during monotherapy treatment

Toxicity	Reduce Temozolomide by 1 dose level[a]	Discontinue Temozolomide
Absolute neutrophil count	< 1.0 x 10^9/l	See footnote b
Thrombocyte count	< 50 x 10^9/l	See footnote b
CTC non-haematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

a: Temozolomide dose levels are listed in Table 2.

b: Temozolomide is to be discontinued if:

• dose level -1 (100 mg/m^2) still results in unacceptable toxicity

• the same Grade 3 non-haematological toxicity (except for alopecia, nausea, vomiting) recurs

after dose reduction.

Adult and paediatric patients 3 years of age or older with recurrent or progressive malignant glioma:

A treatment cycle comprises 28 days. In patients previously untreated with chemotherapy, Temozolomide is administered orally at a dose of 200 mg/m^2 once daily for the first 5 days followed by a 23 day treatment interruption (total of 28 days). In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 once daily, for 5 days if there is no haematological toxicity.

Special populations

Paediatric population

In patients 3 years of age or older, Temozolomide is only to be used in recurrent or progressive malignant glioma. Experience in these children is very limited. The safety and efficacy of Temozolomide in children under the age of 3 years have not been established. No data are available.

Patients with hepatic or renal impairment

The pharmacokinetics of Temozolomide were comparable in patients with normal hepatic function and in those with mild or moderate hepatic impairment. No data are available on the administration of Temozolomide in patients with severe hepatic impairment (Child's Class C) or with renal impairment. Based on the pharmacokinetic properties of Temozolomide, it is unlikely that dose reductions are required in patients with severe hepatic impairment or any degree of renal impairment. However, caution should be exercised when Temozolomide is administered in these patients.

Elderly patients

Based on a population pharmacokinetic analysis in patients 19-78 years of age, clearance of Temozolomide is not affected by age. However, elderly patients (> 70 years of age) appear to be at increased risk of neutropenia and thrombocytopenia.

Method of administration

Temozolomide hard capsules should be administered in the fasting state.

The capsules must be swallowed whole with a glass of water and must not be opened or chewed.

If vomiting occurs after the dose is administered, a second dose should not be administered that day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

Hypersensitivity to dacarbazine (DTIC).

Severe myelosuppression

4.4 Special warnings and precautions for use

Pneumocystis jirovecii pneumonia

Patients who received concomitant Temozolomide and RT in a pilot trial for the prolonged 42-day schedule were shown to be at particular risk for developing *Pneumocystis jirovecii* pneumonia (PCP). Thus, prophylaxis against PCP is required for all patients receiving concomitant Temozolomide and RT for the 42-day regimen (with a maximum of 49 days) regardless of lymphocyte count. If lymphopenia occurs, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1.

There may be a higher occurrence of PCP when Temozolomide is administered during a longer dosing regimen. However, all patients receiving Temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP, regardless of the regimen. Cases of fatal respiratory failure have been reported in patients using Temozolomide, in particular in combination with dexamethasone or other steroids.

Hepatotoxicity

Hepatic injury, including fatal hepatic failure, has been reported in patients treated with Temozolomide. Baseline liver function tests should be performed prior to treatment initiation. If abnormal, physicians should assess the benefit/risk prior to initiating temozolomide including the potential for fatal hepatic failure. For patients on a 42 day treatment cycle liver function tests should be repeated midway during this cycle. For all patients, liver function tests should be checked after each treatment cycle. For patients with significant liver function abnormalities,

physicians should assess the benefit/risk of continuing treatment. Liver toxicity may occur several weeks or more after the last treatment with temozolomide.

Malignancies

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukaemia, have also been reported very.

Anti-emetic therapy

Nausea and vomiting are very commonly associated with Temozolomide.
Anti-emetic therapy may be administered prior to or following administration of Temozolomide.

Adult patients with newly-diagnosed glioblastoma multiforme

Anti-emetic prophylaxis is recommended prior to the initial dose of concomitant phase and it is strongly recommended during the monotherapy phase.

Patients with recurrent or progressive malignant glioma

Patients who have experienced severe (Grade 3 or 4) vomiting in previous treatment cycles may require anti-emetic therapy.

Laboratory parameters

Patients treated with Temozolomide may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medicinal products associated with aplastic anemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, the following laboratory parameters must be met: ANC $\geq 1.5 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until ANC $> 1.5 \times 10^9$/l and platelet count$> 100 \times 10^9$/l. If ANC falls to $< 1.0 \times 10^9$/l or the platelet count is $< 50 \times 10^9$/l during any cycle, the next cycle should be reduced one dose level. Dose levels include 100 mg/m^2, 150 mg/m^2, and 200 mg/m^2. The lowest recommended dose is 100 mg/m^2.

Paediatric population

There is no clinical experience with use of Temozolomide in children under the age of 3 years. Experience in older children and adolescents is very limited.

Elderly patients (> 70 years of age)

Elderly patients appear to be at increased risk of neutropenia and thrombocytopenia, compared with younger patients. Therefore, special care should be taken when Temozolomide is administered in elderly patients.

Male patients

Men being treated with Temozolomide should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

In a separate phase I study, administration of Temozolomide with ranitidine did not result in alterations in the extent of absorption of temozolomide or the exposure to its active metabolite monomethyl triazenoimidazole carboxamide (MTIC).

Administration of Temozolomide with food resulted in a 33 % decrease in C_{max} and a 9 % decrease in area under the curve (AUC).

As it cannot be excluded that the change in C_{max} is clinically significant, Temozolomide should be administered without food.

Based on an analysis of population pharmacokinetics in phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 receptor antagonists, or phenobarbital did not alter the clearance of Temozolomide. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of Temozolomide.

No studies have been conducted to determine the effect of Temozolomide on the metabolism or elimination of other medicinal products. However, since Temozolomide does not undergo hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.

Use of Temozolomide in combination with other myelosuppressive agents may increase the likelihood of myelosuppression.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

There are no data in pregnant women. In preclinical studies in rats and rabbits receiving 150 mg/m^2 Temozolomide, teratogenicity and/or foetal toxicity were demonstrated. Temozolomide should not be administered to pregnant women. If use during pregnancy must be considered, the patient should be apprised of the potential risk to the foetus.

Breast-feeding

It is not known whether Temozolomide is excreted in human milk; thus, breast-feeding should be discontinued while receiving treatment with Temozolomide.

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy while they are receiving Temozolomide.

Male fertility

Temozolomide can have genotoxic effects. Therefore, men being treated with it should be advised not to father a child up to 6 months after receiving the last dose and to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with Temozolomide.

4.7 Effects on ability to drive and use machines

Temozolomide has minor influence on the ability to drive and use machines due to fatigue and somnolence.

4.8 Undesirable Effects

Clinical trial experience

In patients treated with Temozolomide, whether used in combination with RT or as monotherapy following RT for newly-diagnosed glioblastoma multiforme, or as monotherapy in patients with recurrent or progressive glioma, the reported very common adverse reactions were similar: nausea, vomiting, constipation, anorexia, headache and fatigue. Convulsions were reported very commonly in the newly-diagnosed glioblastoma multiforme patients receiving monotherapy, and rash was reported very commonly in newly-diagnosed glioblastoma multiforme patients receiving Temozolomide concurrent with RT and also as monotherapy, and commonly in recurrent glioma. Most haematologic adverse reactions were reported commonly or very commonly in both indications (Tables 4 and 5); the frequency of grade 3-4 laboratory findings is presented after each table.

In the tables undesirable effects are classified according to System Organ Class and frequency. Frequency groupings are defined according to the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Newly-diagnosed glioblastoma multiforme

Table 4 provides treatment-emergent adverse events in patients with newly-diagnosed glioblastoma multiforme during the concomitant and monotherapy phases of treatment.

Table 4. Treatment-emergent events during concomitant and monotherapy treatment phases in patients with newly-diagnosed glioblastoma multiforme

System organ class	Temozolomide + concomitant RT n=288*	Temozolomide monotherapy n=224
Infections and infestations		
Common	Infection, *Herpes simplex*, wound infection, pharyngitis, candidiasis oral	Infection, candidiasis oral
Uncommon		*Herpes simplex*, herpes zoster, influenza–like symptoms
Blood and lymphatic system disorders		

Common	Neutropenia, thrombocytopenia, lymphopenia, leukopenia	Febrile neutropenia, thrombocytopenia, anaemia, leukopenia
Uncommon	Febrile neutropenia, anaemia	Lymphopenia, petechiae
Endocrine disorders		
Uncommon	Cushingoid	Cushingoid
Metabolism and nutrition disorders		
Very common	Anorexia	Anorexia
Common	Hyperglycaemia, weight decreased	Weight decreased
Uncommon	Hypokalemia, alkaline phosphatase increased, weight increased	Hyperglycaemia, weight increased
Psychiatric disorders		
Common	Anxiety, emotional lability, insomnia	Anxiety, depression, emotional lability, insomnia
Uncommon	Agitation, apathy, behaviour disorder, depression, hallucination	Hallucination, amnesia
Nervous system disorders		
Very common	Headache	Convulsions, headache
Common	Convulsions, consciousness decreased, somnolence, aphasia, balance impaired, dizziness, confusion, memory impairment, concentration impaired, neuropathy, paresthesia, speech disorder, tremor	Hemiparesis, aphasia, balance impaired, somnolence, confusion, dizziness, memory impairment, concentration impaired, dysphasia, neurological disorder (NOS), neuropathy, peripheral neuropathy, paresthesia, speech disorder, tremor
Uncommon	Status epilepticus, extrapyramidal disorder, hemiparesis, ataxia, cognition impaired, dysphasia, gait abnormal, hyperesthesia, hypoesthesia, neurological disorder (NOS), peripheral neuropathy	Hemiplegia, ataxia, coordination abnormal, gait abnormal, hyperesthesia, sensory disturbance
Eye disorders		
Common	Vision blurred	Visual field defect, vision blurred, diplopia
Uncommon	Hemianopia, visual acuity reduced, vision disorder, visual field defect, eye pain	Visual acuity reduced, eye pain, eyes dry
Ear and labyrinth disorders		

Common	Hearing impairment	Hearing impairment, tinnitus
Uncommon	Otitis media, tinnitus, hyperacusis, earache	Deafness, vertigo, earache
Cardiac disorders		
Uncommon	Palpitation	
Vascular disorders		
Common	Haemorrhage, oedema, oedema leg	Haemorrhage, deep venous thrombosis, oedema leg
Uncommon	Cerebral haemorrhage, hypertension	Embolism pulmonary, oedema, oedema peripheral
Respiratory, thoracic and mediastinal disorders		
Common	Dyspnoea, coughing	Dyspnoea, coughing
Uncommon	Pneumonia, upper respiratory infection, nasal congestion	Pneumonia, sinusitis, upper respiratory infection, bronchitis
Gastrointestinal disorders		
Very common	Constipation, nausea, vomiting	Constipation, nausea, vomiting
Common	Stomatitis, diarrhoea, abdominal pain, dyspepsia, dysphagia	Stomatitis, diarrhoea, dyspepsia, dysphagia, mouth dry
Uncommon		Abdominal distension, fecal incontinence, gastrointestinal disorder (NOS), gastroenteritis, haemorrhoids
Skin and subcutaneous tissue disorders		
Very common	Rash, alopecia	Rash, alopecia
Common	Dermatitis, dry skin, erythema, pruritus	Dry skin, pruritus
Uncommon	Skin exfoliation, photosensitivity reaction, pigmentation abnormal	Erythema, pigmentation abnormal, sweating increased
Musculoskeletal and connective tissue disorders		
Common	Muscle weakness, arthralgia	Muscle weakness, arthralgia, musculoskeletal pain, myalgia
Uncommon	Myopathy, back pain, musculoskeletal pain, myalgia	Myopathy, back pain
Renal and urinary disorders		
Common	Micturition frequency, urinary incontinence	Urinary incontinence
Uncommon		Dysuria

Reproductive system and breast disorders		
Uncommon	Impotence	Vaginal haemorrhage,menorrhagia, amenorrhea, vaginitis, breast pain
General disorders and administration site conditions		
Very common	Fatigue	Fatigue
Common	Allergic reaction, fever, radiation injury, face oedema, pain, taste perversion	Allergic reaction, fever, radiation injury, pain, taste perversion
Uncommon	Asthenia, flushing, hot flushes, condition aggravated, rigors, tongue discolouration, parosmia, thirst	Asthenia, face oedema, pain, condition aggravated, rigors, tooth disorder
Investigations		
Common	ALT increased	ALT increased
Uncommon	Hepatic enzymes increased, Gamma GT increased, AST increased	

*A patient who was randomised to the RT arm only, received Temozolomide + RT.

Laboratory results

Myelosuppression (neutropenia and thrombocytopenia), which is known dose-limiting toxicity for most cytotoxic agents, including Temozolomide, was observed. When laboratory abnormalities and adverse events were combined across concomitant and monotherapy treatment phases, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed in 8 % of the patients. Grade 3 or Grade 4 thrombocyte abnormalities, including thrombocytopenic events were observed in 14 % of the patients who received Temozolomide.

Recurrent or progressive malignant glioma

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disorders, specifically nausea (43 %) and vomiting (36 %). These reactions were usually Grade 1 or 2 (0 – 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4 %.

Table 5 includes adverse reactions reported during clinical trials for recurrent or progressive malignant glioma and following the marketing of Temozolomide.

Table 5. Adverse reactions in patients with recurrent or progressive malignant glioma	
Infections and infestations	
Rare	Opportunistic infections, including PCP
Blood and lymphatic system disorders	
Very common	Neutropenia or lymphopenia (grade 3-4), thrombocytopenia (grade 3-4)
Uncommon	Pancytopenia, anaemia (grade 3-4), leukopenia
Metabolism and nutrition disorders	
Very common	Anorexia
Common	Weight decrease
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, paresthesia
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea
Gastrointestinal disorders	
Very common	Vomiting, nausea, constipation
Common	Diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus, alopecia
Very rare	Erythema multiforme, erythroderma, urticaria, exanthema
General disorders and administration site conditions	
Very common	Fatigue
Common	Fever, asthenia, rigors, malaise, pain, taste perversion
Very rare	Allergic reactions, including anaphylaxis, angioedema

Laboratory results

Grade 3 or 4 thrombocytopenia and neutropenia occurred in 19 % and 17 % respectively, of patients treated for malignant glioma. This led to hospitalisation and/or discontinuation of Temozolomide in 8 % and 4 %, respectively. Myelosuppression was predictable (usually within the first few cycles, with the nadir between Day 21 and Day 28), and recovery was rapid, usually

within 1-2 weeks. No evidence of cumulative myelosuppression was observed. The presence of thrombocytopenia may increase the risk of bleeding, and the presence of neutropenia or leukopenia may increase the risk of infection.

Gender

In a population pharmacokinetics analysis of clinical trial experience there were 101 female and 169 male subjects for whom nadir neutrophil counts were available and 110 female and 174 male subjects for whom nadir platelet counts were available. There were higher rates of Grade 4 neutropenia (ANC < 0.5 x 10^9/l), 12 % *vs* 5 %, and thrombocytopenia (< 20 x 10^9/l), 9 % *vs* 3 %, in women *vs* men in the first cycle of therapy. In a 400 subject recurrent glioma data set, Grade 4 neutropenia occurred in 8 % of female *vs* 4 % of male subjects and Grade 4 thrombocytopenia in 8 % of female *vs* 3 % of male subjects in the first cycle of therapy. In a study of 288 subjects with newly-diagnosed glioblastoma multiforme, Grade 4 neutropenia occurred in 3 % of female *vs* 0 % of male subjects and Grade 4 thrombocytopenia in 1 % of female *vs* 0 % of male subjects in the first cycle of therapy.

Paediatric population

Oral Temozolomide has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Although the data is limited, tolerance in children is expected to be the same as in adults. The safety of Temozolomide in children under the age of 3 years has not been established.

Post-Marketing Experience

The following additional serious adverse reactions have been identified during post-marketing exposure:

Table 6. Summary of events reported with temozolomide in the post-marketing setting	
Blood and lymphatic system disorders	
Very rare:	prolonged pancytopenia, aplastic anaemia†
Neoplasm benign, malignant and unspecified	

Very rare:	myelodysplastic syndrome (MDS), secondary malignancies, including myeloid leukaemia
Respiratory, thoracic and mediastinal disorders	
Very rare:	interstitial pneumonitis/pneumonitis, pulmonary fibrosis, respiratory failure†
Hepatobiliary disorders*	
Common:	liver enzymes elevations,
Uncommon:	hyperbilirubinemia, cholestasis, hepatitis, hepatic injury, hepatic failure†
Skin and subcutaneous tissue disorders	
Very rare:	toxic epidermal necrolysis, Stevens-Johnson syndrome

† Including cases with fatal outcome

* Frequencies estimated based on relevant clinical trials.

4.9 Overdose

Doses of 500, 750, 1,000, and 1,250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was haematological and was reported with any dose but is expected to be more severe at higher doses. An overdose of 10,000 mg (total dose in a single cycle, over 5 days) was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken the recommended dose for more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, with or without infection, in some cases severe and prolonged and resulting in death. In the event of an overdose, haematological evaluation is needed. Supportive measures should be provided as necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents - Other alkylating agents

ATC code: L01A X03

Mechanism of action

Temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to

the active monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O^6 position of guanine with additional alkylation also occurring at the N^7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Clinical efficacy and safety

Newly-diagnosed glioblastoma multiforme

A total of 573 patients were randomised to receive either Temozolomide + RT (n=287) or RT alone (n=286). Patients in the Temozolomide + RT arm received concomitant Temozolomide (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by monotherapy Temozolomide (150 - 200 mg/m^2) on Days 1 - 5 of every 28-day cycle for up to 6 cycles, starting 4 weeks after the end of RT. Patients in the control arm received RT only.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis was required during RT and combined Temozolomide therapy.

Temozolomide was administered as salvage therapy in the follow-up phase in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22 %) in the Temozolomide + RT arm.

The hazard ratio (HR) for overall survival was 1.59 (95 % CI for HR=1.33 -1.91) with a log-rank $p < 0.0001$ in favour of the Temozolomide arm. The estimated probability of surviving 2 years or more (26 % *vs* 10 %) is higher for the RT + Temozolomide arm. The addition of concomitant Temozolomide to RT, followed by Temozolomide monotherapy in the treatment of patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

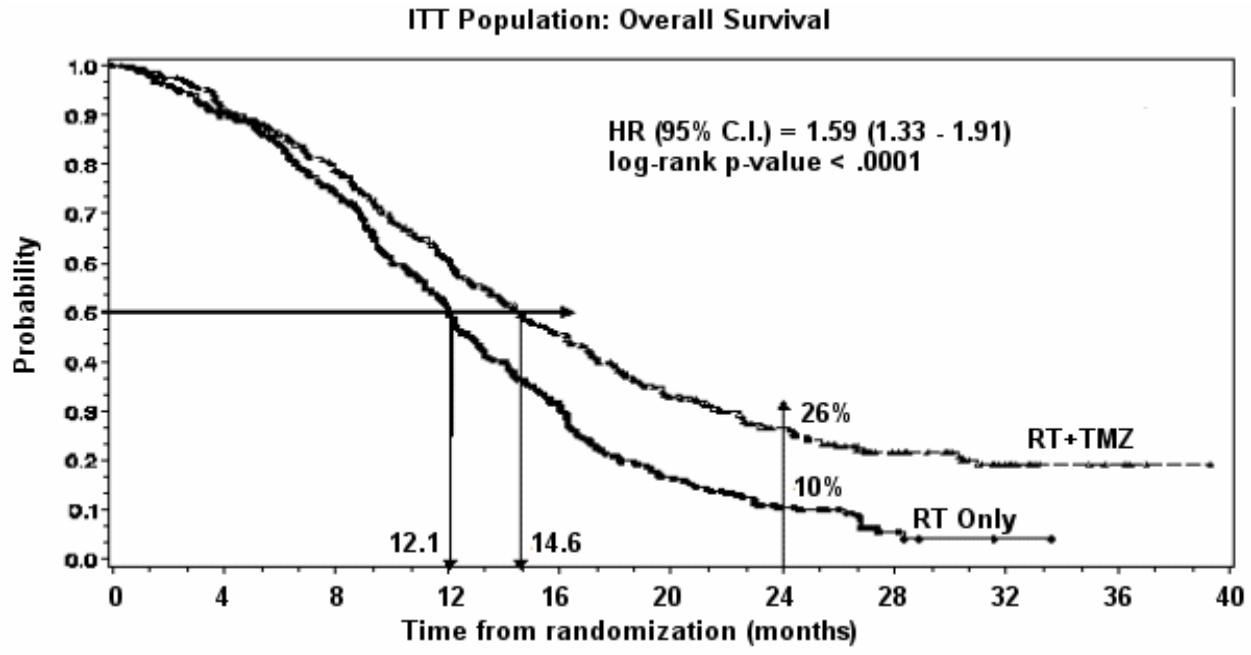

Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] ≥ 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral Temozolomide. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of Temozolomide *vs* procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for Temozolomide than for procarbazine (21 % *vs* 8 %, respectively – chi-square p = 0.008) with median PFS of 2.89 and 1.88 months respectively (log rank p = 0.0063). The median survival

was 7.34 and 5.66 months for Temozolomide and procarbazine, respectively (log rank p = 0.33). At 6 months, the fraction of surviving patients was significantly higher in the Temozolomide arm (60 %) compared with the procarbazine arm (44 %) (chi-square p = 0.019). In patients with prior chemotherapy a benefit was indicated in those with a KPS ≥ 80.

Data on time to worsening of neurological status favoured Temozolomide over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for Temozolomide than for procarbazine (log rank p = < 0.01 to 0.03).

Recurrent Anaplastic Astrocytoma

In a multi-centre, prospective phase II trial evaluating the safety and efficacy of oral Temozolomide in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In 43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral Temozolomide has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to Temozolomide is similar to adults.

5.2 Pharmacokinetic properties

Temozolomide is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O^6 and

N^7 positions of guanine. Relative to the AUC of Temozolomide, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ of MTIC was similar to that of Temozolomide, 1.8 hr.

Absorption

After oral administration to adult patients, Temozolomide is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of ^{14}C-labelled Temozolomide, mean faecal excretion of ^{14}C over 7 days post-dose was 0.8 % indicating complete absorption.

Distribution

Temozolomide demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that Temozolomide crosses the blood-brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of Temozolomide was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ^{14}C elimination is renal. Following oral administration, approximately 5 % to 10 % of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

Special populations

Analysis of population-based pharmacokinetics of Temozolomide revealed that plasma Temozolomide clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate

hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m^2 per cycle both in children and in adults.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

Temozolomide is an embryotoxic, teratogenic and genotoxic alkylating agent. Temozolomide is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of Temozolomide, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose anhydrous (Supertab 21 AN), Sodium starch glycolate (Explotab Low pH), L (+)-Tartaric acid Powder (Emprove®), Hydrophobic Silica, colloidal anhydrous (Aerosil R 972 Pharma), Stearic acid (Speziol L2 SM GF Pharma), EHG capsule Opaque pink cap and opaque white body, size 1 hard gelatin capsules imprinted with “15” on cap and “H” on Body.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30° C and protect from moisture.

6.5 Nature and contents of container

Container pack: 5's Amber glass container pack

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Marketing Authorisation Holder:

Name: **Hetero Labs Limited**

Business Address: 7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar,
Hyderabad-500 018, Andhra Pradesh.

Country: INDIA

Telephone No.: +91-40-23704923/24/25

Fax No.: +91-40-23704926

Manufacturing Site Addresses:

(Company) Name : Hetero Labs Limited (Unit-VI)

Address : APIIC Formulation SEZ, Survey No.410, 411, Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Andhra Pradesh, Andhra Pradesh.

Country : India

Telephone : + 91-08542-202350

Telefax : + 91-08542 238405

E-Mail : drkepi@heterodrugs.com

8. Marketing Authorisation Number

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9. Date of first registration/renewal of the registration

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10. Date of revision of the text
